Swami Ramanand Teerth Marathwada University, Nanded (MS)

A Synopsis Entitled

"Synthesis of Piperazine Carboxamides and Carbamates as Phospolipid inhibitor as a Antimalarial Drug"

Submitted To

Swami Ramanand Teerth Marathwada University, Nanded

For The Degree of

DOCTOR OF PHILOSOPHY IN CHEMISTRY

In the Faculty of

SCIENCE& TECHNOLOGY

By

Mr. Govind N. Shinde
(M.Sc.)

Under The Guidance Of

Dr. Abhay S. Bondge
(Research Guide)
Department of Chemistry
Shivneri Mahavidyalaya, Shirur Anantpal

August 2023

Synthesis of Piperazine Carboxamides and Carbamates as Phospolipid inhibitor as a Antimalarial Drug

Outline of the Proposed Topic of Research

1) Introduction of Proposed Research:

The increased microbial resistance has led to the demand for new bactericidal and fungicidal agents.[1] The reasons for resistance are the inaccurate diagnosis as well as misuse and widespread use of antimicrobial agents.[2] So, a worldwide effort to search for new generation drugs was stimulated to get new potent, resistance free, and safer antimicrobial agents.[3,4]
Endocannabinoids, N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) have been found in most mammalian tissues and they stimulate cannabinoid CB1 and CB2 receptor activity thereby modulating several physiological responses, including nociception, anxiety, and depression[5,6] The two main enzymes involved in endocannabinoid degradation are monoacylglycerol lipase (MAGL) and fatty acid amide hydrolase (FAAH). Two additional endocannabinoid-hydrolyzing enzymes have recently been discovered: a/b-hydrolase domain containing serine hydrolases ABHD6 and ABHD12, which are described as complementary 2-AG-degrading enzymes in the brain.[7] Inhibition of these enzymes leads to accumulation of endocannabinoids and inducement of cannabimimetic effects.[8]

FAAH is the primary AEA-degrading enzyme,[9] but it is also capable of hydrolyzing other bioactive N-acylethanolamines (NAEs), such as N-palmitoylethanolamine (PEA),[10] N-oleoylethanolamine (OEA)[10] and the sleep-inducing lipid oleamide.[11] Pharmacological inhibition of FAAH has been considered as potential therapeutic approach for the treatment of several nervous system disorders, including pain, inflammation, anxiety, and depression.[6,12,13]

MAGL inhibitorsmay have therapeutic potential in treatment of cancer and neuroinflammatory diseases. MAGL hydrolyzes 2-AG to arachidonic acid, from which cyclooxygenases can synthesize neuroinflammatory prostaglandins.[14] Therefore, it is possible that inhibition of MAGL may be an alternative way to regulate prostaglandin production and to reduce inflammation in neurodegenerative diseases. In addition, MAGL has been shown to

control lipid metabolism in cancer cells by promoting production of lipid molecules towards oncogenic lipid messengers.[15]

2) Literature review of the proposed topic:

A large number of FAAH inhibitors have been described over the years, such as a keto heterocycles, lactams, carbamates, and piperidine/piperazine based ureas.[16] So far, the most promising irreversible FAAH inhibitors with respect to selectivity and potency are piperidine and piperazine urea compounds, such as PF-3845 and JNJ-1661010 (**Fig. 1**). The development of potent and selective MAGL inhibitors has been slower compared to that of FAAH due to only recent availability of X-ray crystal structural data.[17–19] In the model by Sanofi-Aventis, the crystal structure of MAGL was built by complexing the enzyme with the piperazine triazole urea inhibitor SAR629.[18] This structure was one starting point for our compound series of piperazine triazole urea compounds. Very recently, remarkable progress has been achieved in the discovery of potent and selective MAGL inhibitors. Cravatt and co-workers have reported MAGL selective piperidine carbamate based inhibitors JZL184 and KLM-29 and piperazine carbamate based dual FAAH–MAGL inhibitors, such as JZL195 (Fig. 1). Other very recently published piperidine/piperazine ureas are benzotriazol-1-ylcarboxamides, such as ML30 (Fig. 1) by Lambert and co-workers[20] and piperazine ureas (e.g., 60j) by Kono et al.[21,22] While writing this manuscript, Wilson and co-workers have reported radiosynthesis of carbamate- and urea-based MAGL inhibitors.[23]

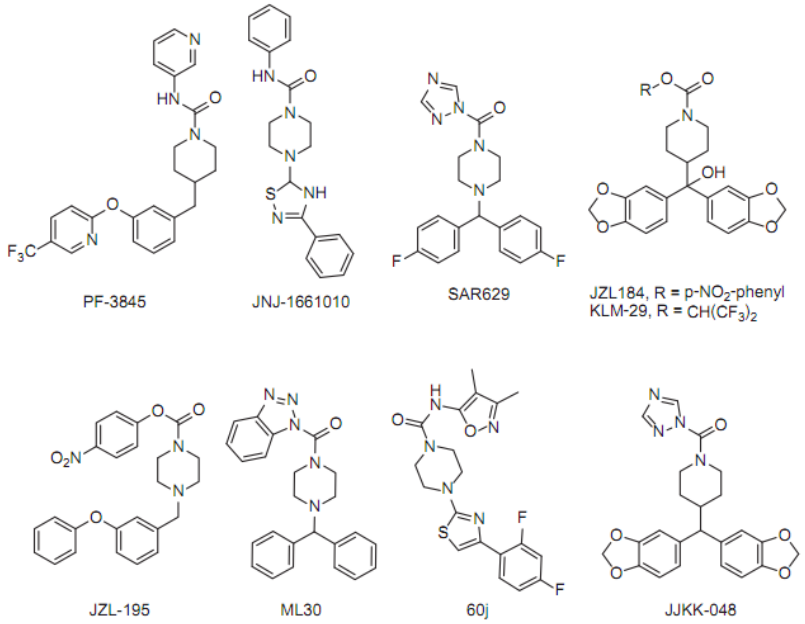
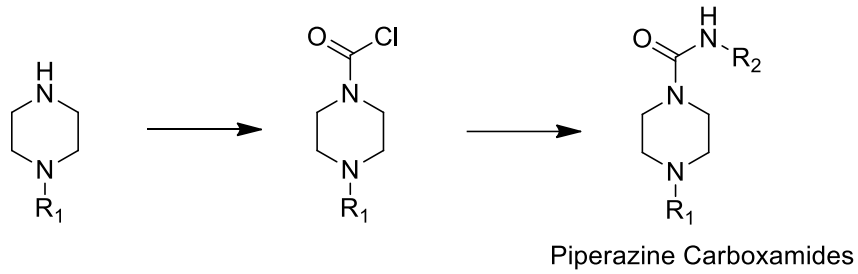
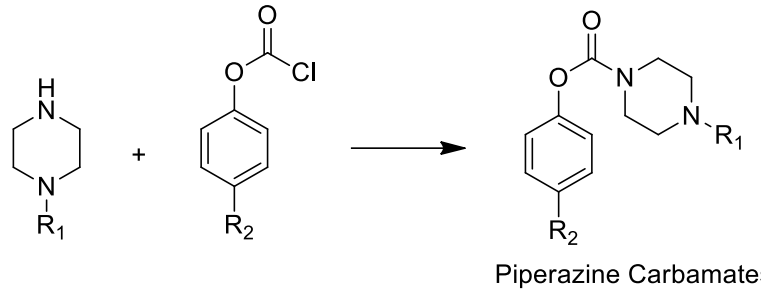


Figure 1. Structures of FAAH and MAGL inhibitors.

Previously it was found that piperazine and piperidine triazole ureas as highly potent and MAGL-selective inhibitors culminating in the synthesis of JJKK-048, which appeared the most potent and MAGL selective inhibitor currently described (IC_{50} < 0.4 nM).[24] Here, we describe the further optimization of piperazine and piperidine carboxamides and carbamates as potent and selective MAGL/FAAH inhibitors or as dual FAAH/MAGL inhibitors.



Scheme 1: Synthesis of 4-substituted Piperazin-1-yl carboxamides



Scheme 2: Synthesis of 4-substituted Piperazine Carbamate

3) Gaps in the existing research:

The literature survey reveals that Piperazine Carboxamides and Carbamates derivatives are reported. The reported compounds have some drawbacks in their synthesis and biological activities. The molecular hybridization technique has been utilized for getting better bioactive compounds. Hence, we have decided to synthesize new Piperazine Carboxamides and Carbamates derivatives to obtain better molecular hybrid bioactive derivatives.

4) Statement of proposed problem:

Motivated by the aforementioned findings, and upon continuation of our research programme in the field of discovery of hybrid heterocyclic compounds bearing biological activities, we have planned to synthesis Piperazine Carboxamides and Carbamates as promising bioactive compounds.

5) Scope of research work:

All these studies will provide us a nice opportunity for learning a lot of new basic and applied chemistry not just from our work but also from the vast literature in this field. We also feel that the approaches which we will be developing quite general and biogenetic in nature and would be useful in designing several important complex natural products and natural product hybrids for structure activity relationship studies. In our opinion, Piperazine Carboxamides and Carbamate derivatives would serve as a launching pad to fight against various new generation diseases.

6) Relevance of the research work:

The results obtained during the proposed reaserch will be useful for further study to obtain novel synthtic bioactive Piperazine Carboxamides and Carbamate hybrids. This will be useful to treat the patients suffering from malaria diseases.

7) Significance of proposed problem:

The present research will be helpful to invent better Piperazine Carboxamides and Carbamates hybrids having excellent antimalarial activity.

8) Objectives of the proposed research:

1) Development of new methods for the synthesis of new Piperazine Carboxamides and Carbamate hybrids.
2) Characterization of newly Piperazine Carboxamides and Carbamate hybrids.
3) The biological screening of new Piperazine Carboxamides and Carbamate hybrids.

9) Hypotheses / Assumptions:

During the Ph. D. work, we have planned to synthesize new Piperazine Carboxamides and Carbamate hybrids. The structural characterization of newly synthesized derivatives will be performed. These newly synthesized compounds will be evaluated for their biological activities (Antimalarial). We are expecting to obtain new Piperazine Carboxamides and Carbamate hybrids possessing good biological activities.

10) Research Methodology:

a. Methods of research:

The major part of the research will be performed in chemistry laboratory. The new Piperazine Carboxamides and Carbamate hybrids will be synthesized in laboratory. The structures of the synthesized intermediates and final compounds will be confirmed by different spectral techniques. The purified compounds will be screened for their biological activities (Antimalarial).

b. Sampling design:

During the synthesis of Piperazine Carboxamides and Carbamate hybrids, 10-15 derivatives of each series will be synthesized and evaluated for their biological significance.

c. Conceptual framework if any:

The literature survey reveals that the Piperazine Carboxamides and Carbamate containing compounds possessing good biological activities. The new Piperazine Carboxamides and Carbamate molecular hybrids will be playing crucial role for possessing biological activities.

d. Research design (Explanation of how research is being conducted and the tools tobe used for the same):

The synthesis of Piperazine Carboxamides and Carbamate hybrids will be initiated by doing the literature survey and studying the MSDS of all chemicals to be utilized during synthesis. Each compound and intermediates will be synthesized in laboratory. The purification of these will be done either recrystallization or column chromatography. The spectral analysis of each purified compounds will carried out. The biological screening of each Piperazine Carboxamides and Carbamate hybrid will be performed.

e. Methods of data collection:

All the Piperazine Carboxamides and Carbamate hybrids will be synthesized in chemistry laboratory.

f. Methods of data analysis (Use of parametric and non-parametric tools andtechniques as case may be):

Major data analysis will be performed in laboratory. Few of the spectral data will collected from outside institutes.

g. Details of equipment's and instruments to be used and their source (Available inresearch center or facility is to be hired from other center / institute / laboratoryetc):

For performing the proposed research, the major equipments and instruments are available in chemistry department laboratory. The spectral analysis like ^{1}H, ^{13}C NMR and HRMS will be hired from other institutes like CDRI, NCL, IICT etc.

11) Chapter Scheme:

i) Introduction
ii) Review of literature
iii) Material and methods
iv) Experimental results
v) Discussion
vi) Summary and conclusion
vii) Bibliography

12) Expected outcome:

From the proposed research, we are expecting to obtain some novel bioactive Piperazine Carboxamides and Carbamate hybrids possessing good biological activities.

13) Plan of work (Time schedule of activity):

i) 0-6 Months: The literature survey and purchase of required chemical and glasswares.
ii) 7-24 Months: The heterocyclic compounds preparation and characterization.
iii) 25-30 Months: The biological screening and publication of results obtained.
iv) 31-36 Months: Writing of PhD Thesis and submission to the University.

14) References and Bibliography:

1. Naeem A, Badshah SL, Muska M, et al. The current case of quinolones: synthetic approaches and antibacterial activity. Molecules 2016;21:268.
2. Welte T, Pletz MW. Antimicrobial treatment of nosocomial meticillin-resistant Staphylococcus aureus (MRSA) pneumonia: current and future options. Int J Antimicrob Agents 2010;36:391–400.
3. Frere JM. Beta-lactamases and bacterial resistance to antibiotics. Mol Microbial 1995;16: 385–95.

4. Devasahayam G, Scheld WM, Hoffman PS. Newer antibacterial drugs for a new century. Expert Opin Invest Drugs 2010;19:215–34.
5. Cravatt, B. F.; Lichtman, A. H. J. Neurobiol. 2004, 61, 149.
6. Hill, M. N.; Gorzalka, B. B. CNS Neurol. Disord. Drug Targets 2009, 8, 451
7. Savinainen, J. R.; Saario, S. M.; Laitinen, J. T. Acta Physiol. 2012, 204, 267.
8. Ahn, K.; McKinney, M. K.; Cravatt, B. F. Chem. Rev. 2008, 108, 1687
9. Giang, D. K.; Cravatt, B. F. Proc. Natl. Acad. Sci. U.S.A. 1997, 94, 2238.
10. Fowler, C. J.; Jonsson, K.; Tiger, G. Biochem. Pharmacol. 2001, 62, 517.
11. Patricelli,M. P.; Patterson, J. E.; Boger, D. L.; Cravatt, B. F. Bioorg. Med. Chem. Lett. 1998, 8, 613.
12. Kinsey, S. G.; Long, J. Z.; Cravatt, B. F.; Lichtman, A. H. J. Pain 2010, 11, 1420.
13. Hill, M. N.; Hillard, C. J.; Bambico, F. R.; Patel, S.; Gorzalka, B. B.; Gobbi, G. Trends Pharmacol. Sci. 2009, 30, 484
14. Nomura, D. K.; Morrison, B. E.; Blankman, J. L.; Long, J. Z.; Kinsey, S. G.; Marcondes, M. C. G.; Ward, A. M.; Hahn, Y. K.; Lichtman, A. H.; Conti, B.; Cravatt, B. F. Science 2011, 334, 809.
15. Nomura, D. K.; Long, J. Z.; Niessen, S.; Hoover, H. S.; Ng, S.; Cravatt, B. F. Cell 2010, 140, 49.
16. Otrubova, K.; Ezzili, C.; Boger, D. L. Bioorg. Med. Chem. Lett. 2011, 21, 4674.
17. Labar, G.; Bauvois, C.; Borel, F.; Ferrer, J.; Wouters, J.; Lambert, D. M. ChemBioChem 2010, 11, 218.
18. Bertrand, T.; Augé, F.; Houtmann, J.; Rak, A.; Vallée, F.; Mikol, V.; Berne, P. F.; Michot, N.; Cheuret, D.; Hoornaert, C.; Mathieu, M. J. Mol. Biol. 2010, 396, 663
19. Schalk-Hihi, C.; Schubert, C.; Alexander, R.; Bayoumy, S.; Clemente, J. C.; Deckman, I.; DesJarlais, R. L.; Dzordzorme, K. C.; Flores, C. M.; Grasberger, B.; Kranz, J. K.; Lewandowski, F.; Liu, L.; Ma, H.; Maguire, D.; Macielag, M. J.; McDonnell, M. E.; Mezzasalma Haarlander, T.; Miller, R.; Milligan, C.; Reynolds, C.; Kuo, L. C. Protein Sci. 2011, 20, 670.
20. Morera, L.; Labar, G.; Ortar, G.; Lambert, D. M. Bioorg. Med. Chem. 2012, 20, 6260.
21. Kono, M.; Matsumoto, T.; Kawamura, T.; Nishimura, A.; Kiyota, Y.; Oki, H.; Miyazaki, J.; Igaki, S.; Behnke, C. A.; Shimojo, M.; Kori, M. Bioorg. Med. Chem. 2013, 21,28.

22. Kono, M.; Matsumoto, T.; Imaeda, T.; Kawamura, T.; Fujimoto, S.; Kosugi, Y.; Odani, T.; Shimizu, Y.; Matsui, H.; Shimojo, M.; Kori, M. Bioorg. Med. Chem. 2014, 22, 1468.
23. Hicks, J. W.; Parkes, J.; Tong, J.; Houle, S.; Vasdev, N.; Wilson, A. A. Nucl. Med. Biol. 2014, 41, 688.
24. Aaltonen, N.; Savinainen, J.; Ribas, C.; Rönkkö, J.; Kuusisto, A.; Korhonen, J.; Navia-Paldanius, D.; Häyrinen, J.; Takabe, P.; Käsnänen, H.; Pantsar, T.; Laitinen, T.; Lehtonen, M.; Pasonen-Seppänen, S.; Poso, A.; Nevalainen, T.; Laitinen, J. Chem. Biol. 2013, 20, 379.

Mr. Govind N. Shinde
Research Student

Dr. Abhay S. Bondge
Research Guide